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Targeting Ligand-Dependent and Ligand-Independent Androgen
Receptor Signaling in Prostate Cancer

PRINCIPAL INVESTIGATOR:
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14. ABSTRACT

We have made significant progress in our work with peptidomimetics targeting ligand-dependent and ligand-independent androgen receptor signaling in prostate Cancer. We have designed, created, tested and validated 23 analogues of our lead compound and have identified chemistries that are optimal for peptidomimetic stability, potency and selectivity. Towards this end, we first established a highly efficient synthetic protocol to generate these compounds. From our testing we identified several compounds with promising activities that are currently under investigation for in-depth analysis and that will help refine the next generation of more potent peptidomimetics. We have further refined our genomic signaling assays to reflect what is currently known about AR-driven signaling in prostate cancer and have shown that the peptidomimetics block both ligand-dependent and ligand-independent androgen receptor signaling. Importantly, we have shown that these peptidomimetics are orally bioavailable and biologically active. Finally, we have published several manuscripts, including one in Nature Communications on our lead D2 compound and its remarkable functional activity in prostate cancer cell lines. In the coming year, we intend to build on our accomplishments and further develop the peptidomimetics as biologically usable compounds.

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Introduction

The androgen receptor (AR) is critical in the normal development and function of the prostate, as well as in prostate carcinogenesis1. Androgen deprivation therapy is the mainstay in treatment of advanced prostate cancer (PCa); however, after an initial response, the disease inevitably progresses to castration-resistant PCa (CRPC)2. Recent evidence suggests that continued AR activation, either in a ligand-dependent (LD) or in a ligand-independent (LI) manner, is commonly associated with CRPC1. There is an unmet need for novel agents to target both LI and LD AR signaling in CRPC. Our overarching hypothesis is that the disruption of interactions between AR and critical cofactors by targeting structural motifs involved in protein-protein interactions (PPIs) may block both LD and LI activation of AR and represent a novel therapeutic approach for patients with CRPC.

In this grant, we had proposed to design and synthesize peptidomimetics that can more specifically disrupt LD and LI activation of AR. We then wanted to evaluate the mechanism of specific peptidomimetics in blocking AR signaling. Finally, we wanted to evaluate the utility of specific peptidomimetics in animal models and on primary PCa tissue. In our first year, we have made significant strides in these endeavors. We have created and tested more than 23 variants of the peptidomimetics and have learned to build a better more potent peptidomimetic.

Body

In this grant, our overall goals were to target the androgen receptor in prostate cancer using peptidomimetics for the LxxLL and WxxLF motif using oligo-benzamide scaffolds that are highly specific for and can disrupt the AR-PELP-1 interaction.

We have had a highly productive year and have made significant strides in our work with peptidomimetics. Towards this end, we have published a critical manuscript in Nature Communications (Ravindranathan et al, Nature Communications 2013) that outlines our work with our leading D2 compound and its remarkable activities on prostate cancer cell lines. This manuscript has been well-received and has invited significant collaborations to further explore these agents. We have further worked on our peptidomimetics and refined their activities.
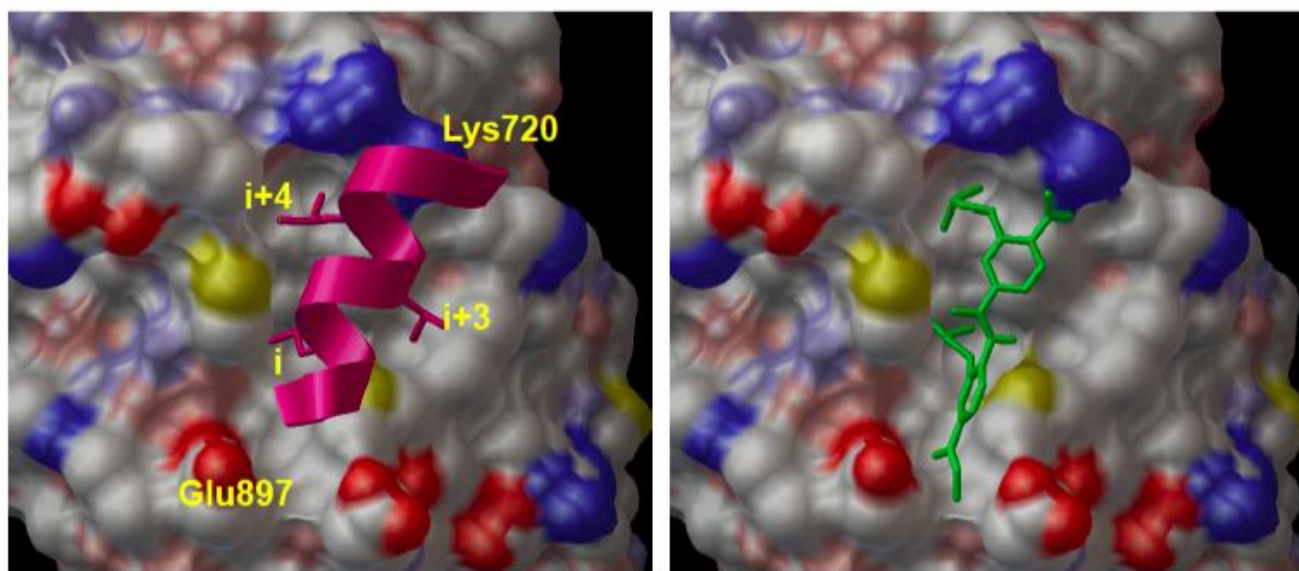

Model showing the docking of the D2 peptidomimetic with the androgen receptor in a helical conformation (pink ribbon, left panel) and in the native structure (green stick figure, right panel) (Ravindranathan et al, Nature Communications 2013).

To further improve the specificity of D2 for AR-PELP1 interaction, we have evaluated the flanking residues of the LxxLL motifs on PELP1. Shown below is the flanking sequences of each of the 10 LxxLL motifs on PELP1 with sequences at -3 and -4 and +7 being targeted for tris-bemzamide development.

#	Position of LxxLL						-4	-3			i			+3	+4			+7							
1	33-37	G	L	S	A	V	S	S	G	P	R	L	R	L	L	L	L	E	S	V	S	G	L	L	Q	P
2	69-73	P	N	R	S	A	P	H	L	P	G	L	M	C	L	L	R	L	H	G	S	V	G	G	A	Q
3	111-115	S	I	K	T	R	P	E	G	L	C	L	L	S	L	L	V	G	E	S	P	T	E	L	F	Q
4	155-159	P	A	T	M	E	L	A	V	A	V	L	R	D	L	L	R	Y	A	A	Q	L	P	A	L	F
5	181-185	D	I	S	M	N	H	L	P	G	L	L	T	S	L	L	G	L	R	P	E	C	E	Q	S	A
6	264-268	L	K	H	T	E	S	W	E	Q	E	L	H	S	L	L	A	S	L	H	T	L	L	G	A	L
7	271-275	E	Q	E	L	H	S	L	L	A	S	L	H	T	L	L	G	A	L	Y	E	G	A	E	T	A
8	364-368	K	N	I	S	L	H	G	D	G	P	L	R	L	L	L	L	P	S	I	H	L	E	A	L	D
9	459-463	L	Q	G	G	A	S	G	E	A	L	L	T	H	L	L	S	D	I	S	P	P	A	D	A	L
10	579-583	P	Y	T	S	S	R	C	R	R	E	L	Y	C	L	L	L	A	L	L	L	A	P	S	P	R

We have designed tris-benzamide-based molecules to introduce additional functional group from the flanking residues around the LXXLL motif to our lead D2 compound.
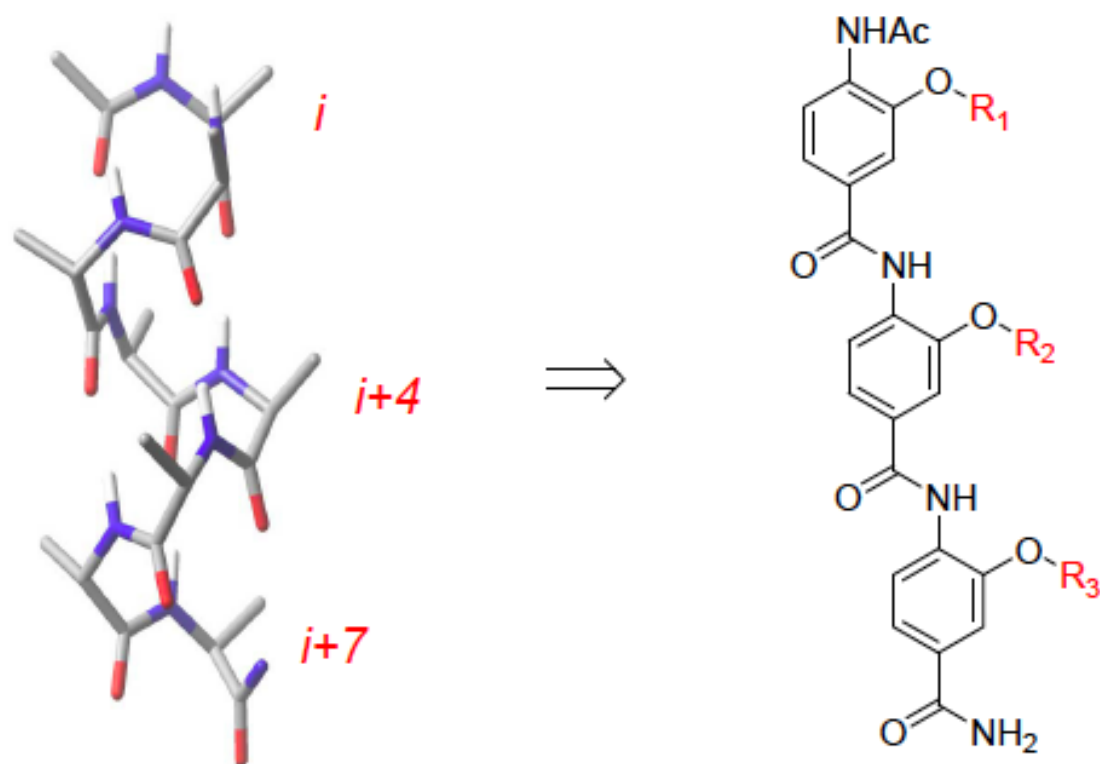
Left side of the figure shows lowest energy conformation of tris benzamides and the right side shows the basic chemical structure of trisbenzamides. Tris-benzamides represents a rigid scaffold to place three side chain groups (R1, R2 and R3). These tris-benzamides emulate one side of a helix (two helical turns) and represent a larger molecule than bis-benzamides that have only two side chain groups (R1 and R2). The larger molecules are likely to have a greater degree of specificity for specific protein-protein interactions.

* To facilitate the synthesis of tris-benzamide analogues designed to target AR, we have first established the synthetic procedure that allowed us to produce a number of molecules. This standard operating protocol has dramatically enhanced our ability to generate a number of molecules. This synthetic procedure has been detailed in our Nature Communications publication.
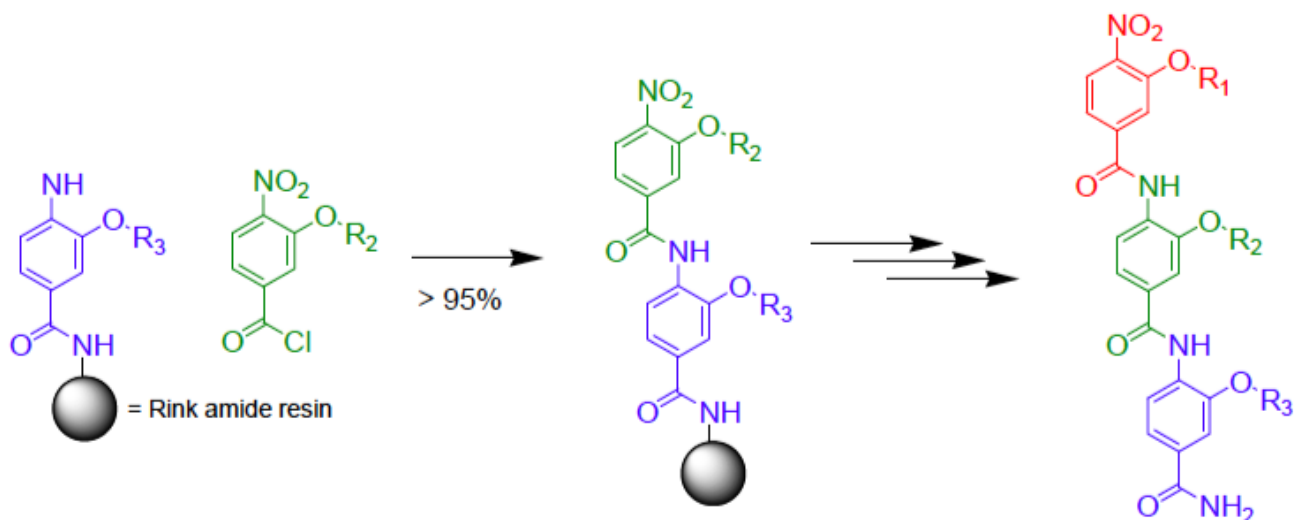
Using a rink amide resin and solid phase synthesis, we have been able to decrease the number of steps in the

synthesis of tris-benzamides to four easy steps. These steps are characterized by high-efficiency (>95%) enabling rapid synthesis of the tris-benzamides. This was a dramatically improved synthesis than our earlier synthetic plan outlined in Ahn and Han, Tetrahedron letters 2007, shown below.

Synthesis of Tris-Benzamides
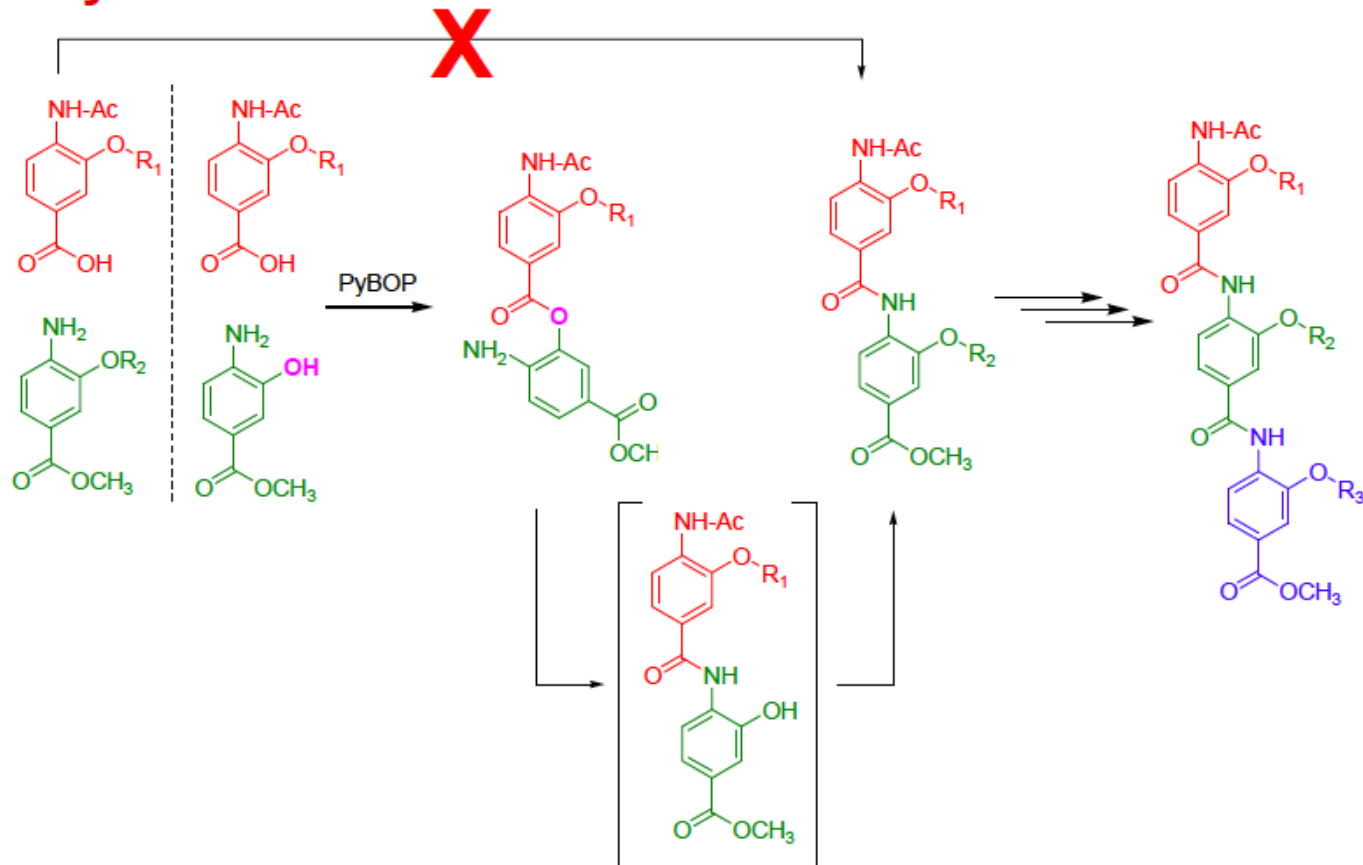
Ahn and Han, *Tetrahedron Lett.* **2007**, *48*, 3543

* Following the established synthetic protocol, we have synthesized 23 tris-benzamide analogues derived from the leading TKD2 compound. These compounds were individually evaluated for optimal characteristics by 2-D NMR, stability and toxicity studies prior to full scale studies. Four of these active compounds are depicted below.

7
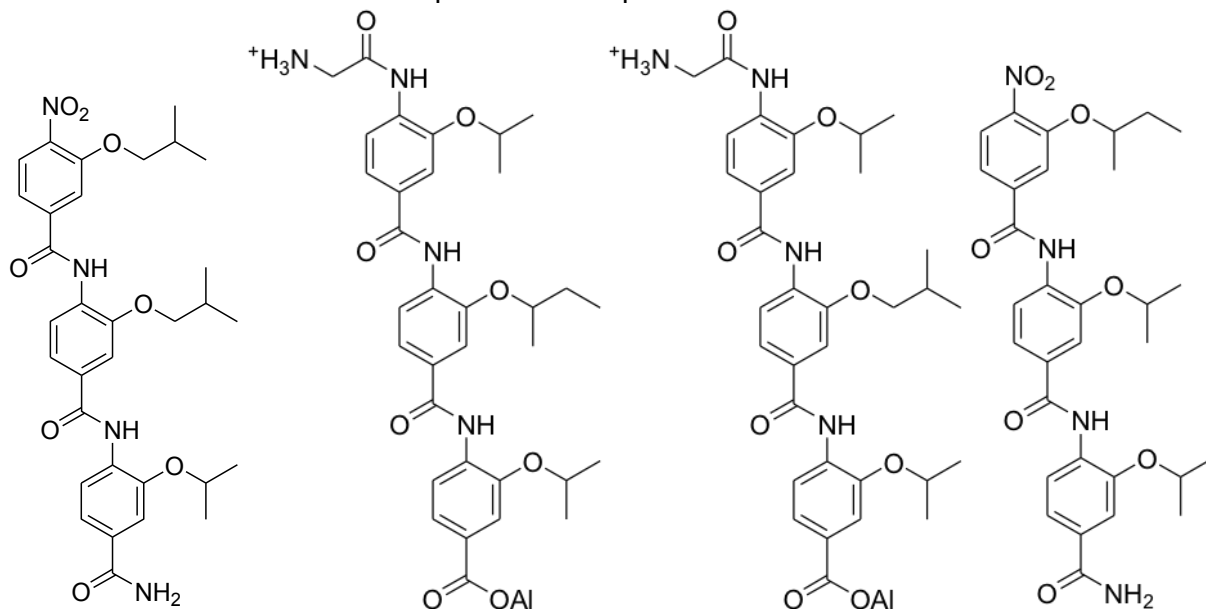
These tris-benzamide compounds were examined for their inhibitory activities on cell proliferation and AR function using LNCaP cell line. We found that several molecules had activity comparable to D2: with these modifications, we have gone back to the synthetic procedure to generate more potent modifications. We have a better sense of how each modification of D2 affects its potency and function.
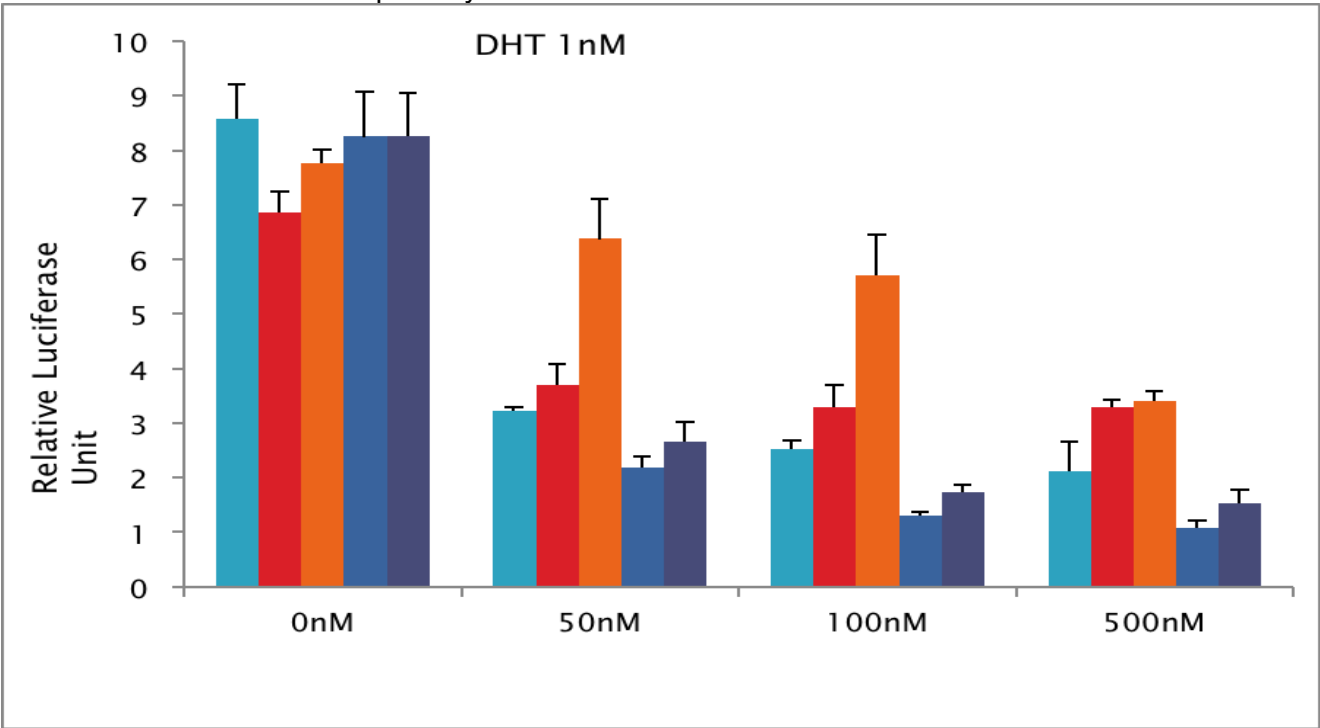

Luciferase assay shows effect of increasing concentrations of various peptidomimetics (each color depicts a distinct tris-benzamide) on the relative DHT-induced transcription from a ARE-luciferase construct in prostate cancer cells. These peptidomimetics were incubated with cells prior to treatment with DHT.
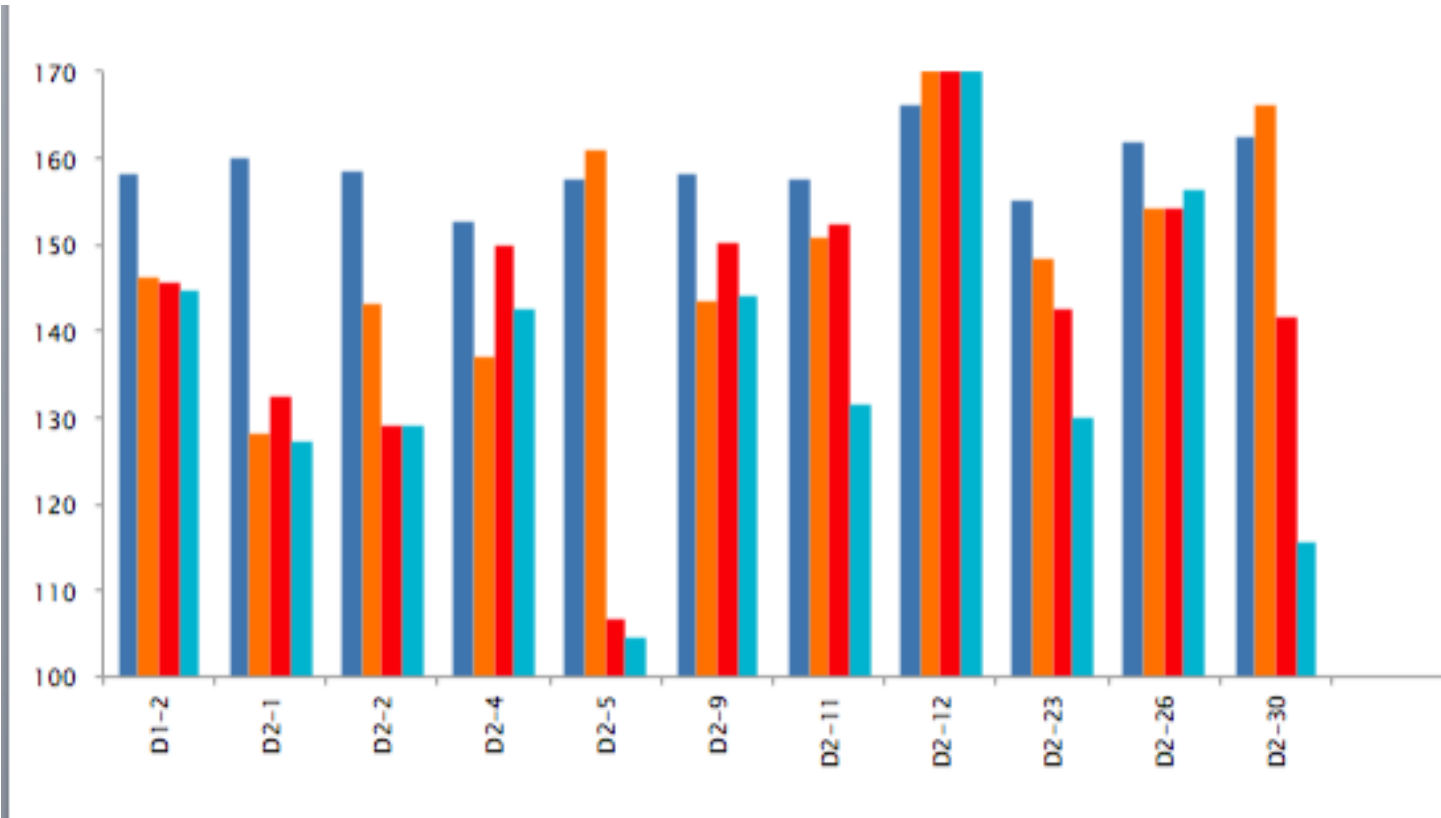
Increasing concentrations of active tris-benzamide agents were then evaluated for their effect on proliferation of C4-2 prostate cancer cells. The most biologically active compounds were evaluated for toxicity in multiple cell lines and found to be non-toxic.

* Active tris-benzamide compounds underwent further confirmation in vivo using coimmunoprecipitation experiments for their ability to disrupt AR-PELP1 complex formation. We
have now agents that disrupt more selective classes of LxxLL motifs: for example, we have compounds that can block AR-PELP1 and AR-hsp27 interaction through the LxxLL motif as well as compounds that only block AR-PELP1 (and not AR-hsp27). We believe that these compounds will be critical for ascertaining the biological effect of the targets.
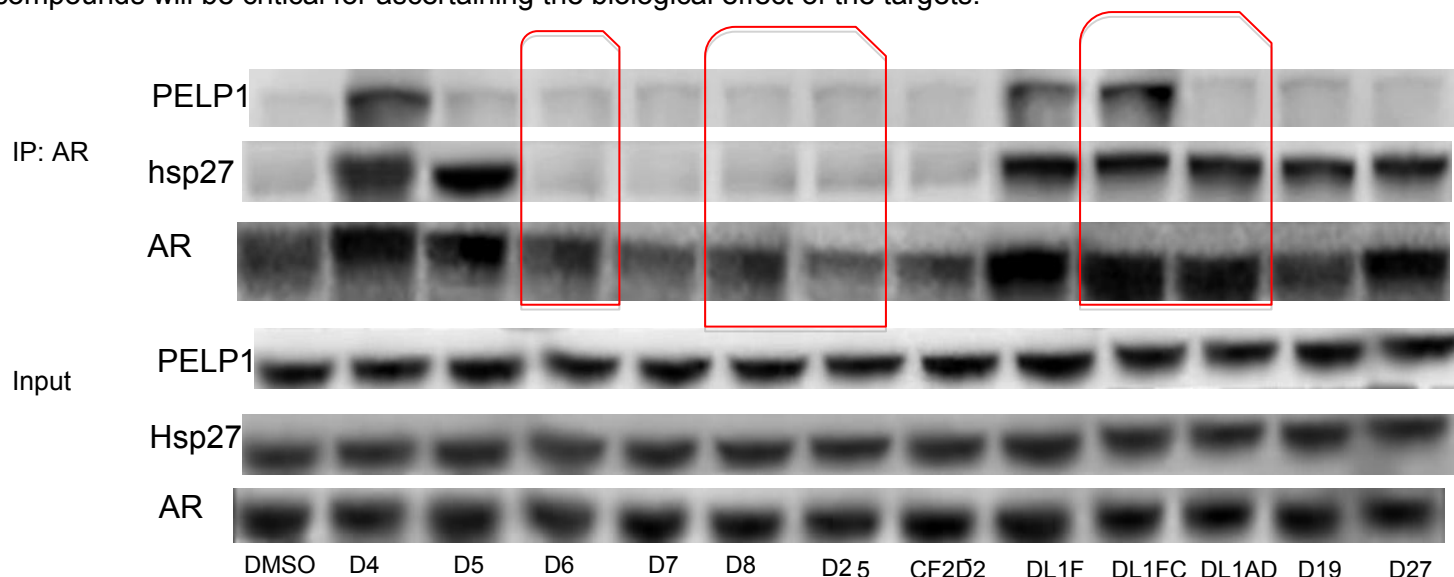
Coimmunoprecipitation between AR and PELP1 in the presence of various peptidomimetics shows differential effect on their ability to block AR-PELP1 interaction. (loss of interaction in first panel signifies activity of the peptidomimetic). These are ongoing experiments and a representative experiment is shown.

From our studies to date, we have identified several compounds (D5, D7, D8, DL1FC, DL1AD) with promising activities on AR signaling that are currently under investigation for in-depth analysis. We believe that these compounds have better activity than D2 but still work in the 20-50 nM range. We are using structure function studies to further optimize these trisbenzamides to achieve agents in the sub 10nM range efficacy.

Our primary objective was to establish a series of compounds blocking the AR ligand-dependent and ligand-independent gene expression. We have retooled our efforts to make peptidomimetics more potent first and then use this knowledge to create more potent drugs to target AR. We believe that optimizing the fit of peptidomimetics to the AR, that we can use the lessons learned in drug design to make more efficient peptidomimetics.
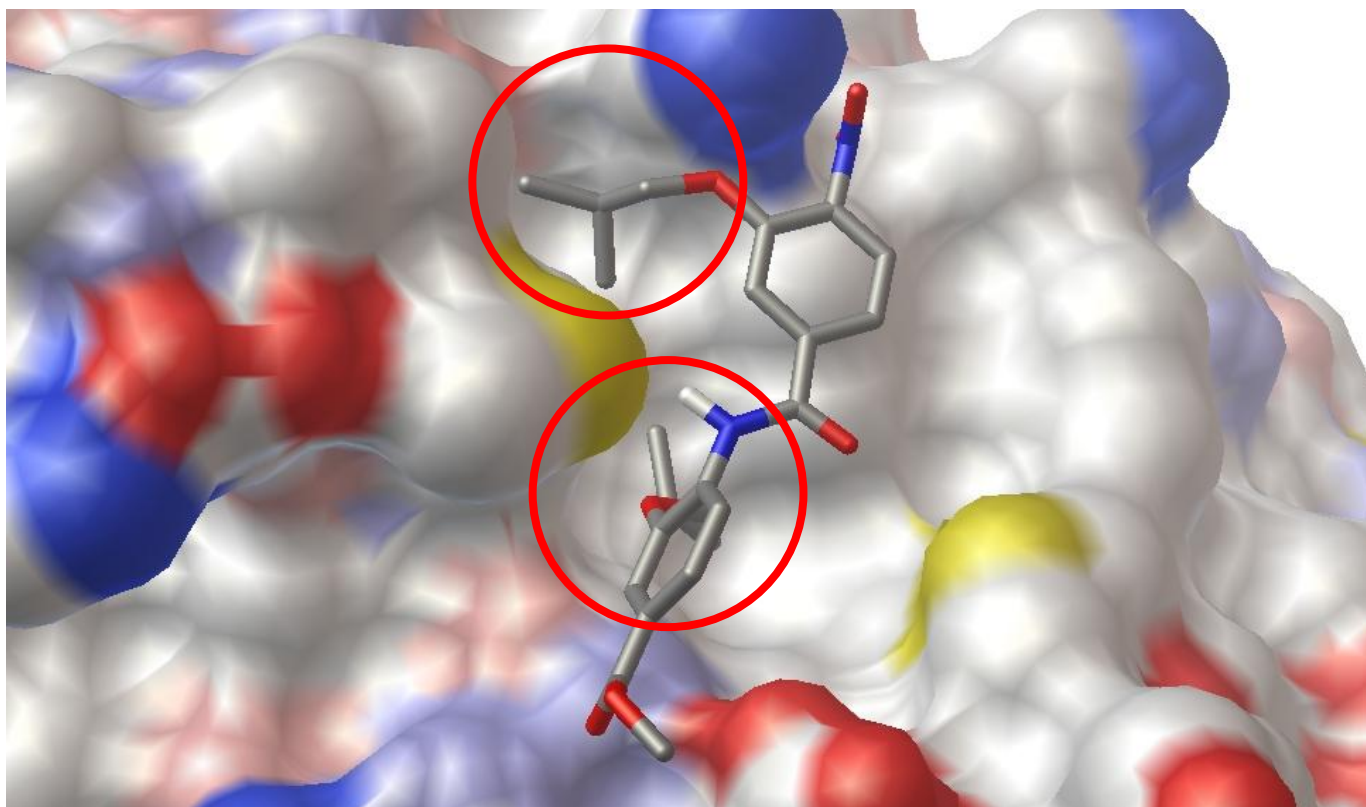
Planned structural modifications of D2-derived peptidomimetics by docking studies using AutoDock. The circled areas represent areas of D2 modified to better fit with the androgen receptor shown.

We have refined and our panel of AR driven genes to be more comprehensive and more in line with what is currently known about AR-driven signaling in prostate cancer. We have developed a robust panel of genes for AR signaling that is reflective of the clinical findings in both ligand dependent and ligand-independent androgen receptor signaling.

* We are currently evaluating the effect of the leading trisbenzamide variants on AR driven proliferation in larger number of prostate cancer cell lines, including those driven by AR splice variants.

* We are currently evaluating the effect of trisbenzamide variants on AR genomic signaling in a multitude of cell lines, including the effect on Ligand-dependent and ligand-independent activity using Q-PCR and ChIP analyses. We will use RNA-seq and ChiP-seq analyses rather than microarray in the upcoming months to validate findings for the most active peptidomimetic.

* We have evaluated some peptidomimetics in animal models and have found similar levels of activity. An interesting finding is that these peptidomimetics are orally bioavailable with a half-life of 4 hours. We are further evaluating the effect of these agents on the growth of xenografts.
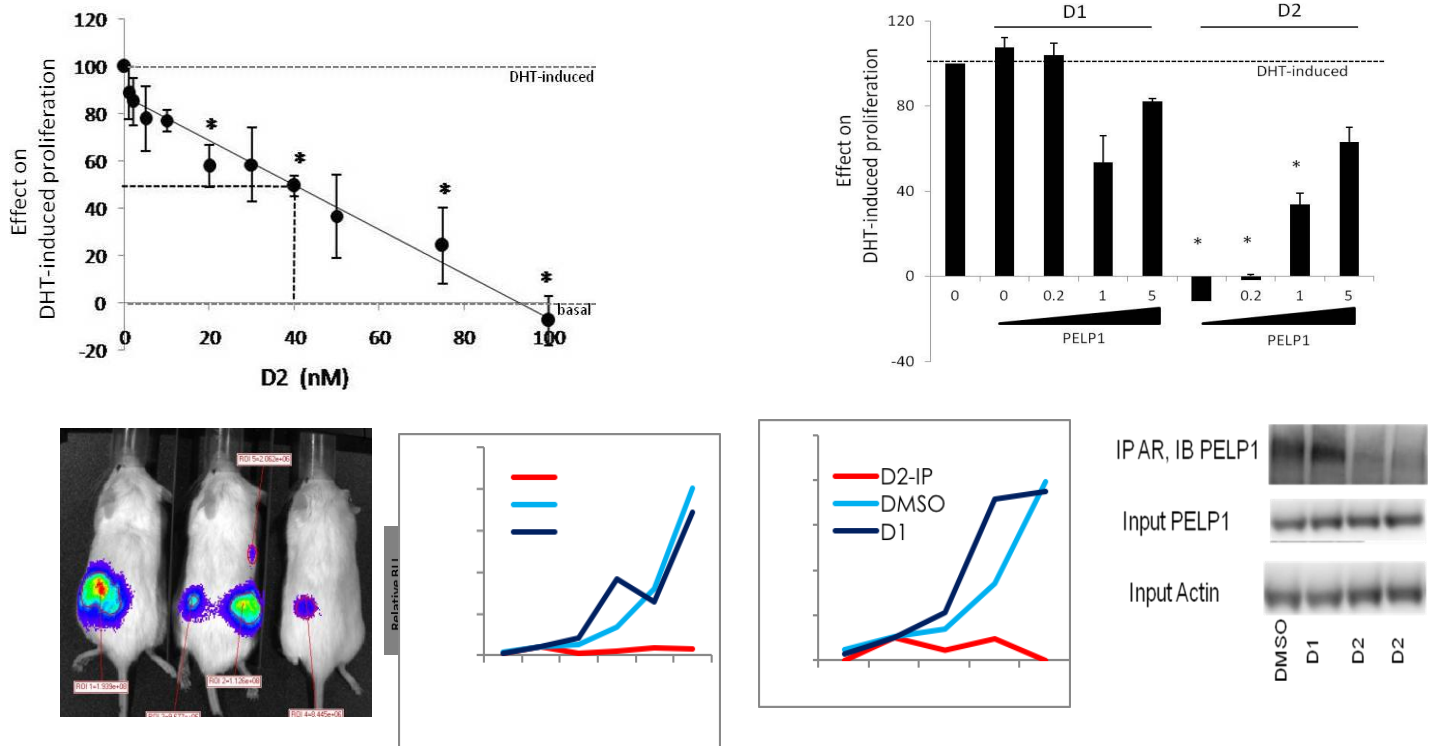
D2 inhibits prostate cancer cell growth in vitro and in vivo. (a) A panel of prostate cancer cells pretreated with DMSO, 100nM D1 or D2 for 2 h before 10 nM DHT treatment for 72 h were assessed by MTTproliferation assay. Data were normalized to the DMSO treatment for each cell line. (b) Effect of pretreatment with 100nM of D1 and D2 on DHT-induced proliferation in LNCaP cells by CyQuant assay. (c) Dose–response curve of D2 on the proliferation of LAPC4 cells. (d) Rescue of DHT-induced proliferation by overexpression of PELP1 by transfecting LNCaP cells with increasing amounts of pPELP1-GFP following suppression with 100nM D2. (e) Subcutaneous C4-2 tumours were allowed to establish in SCID mice until palpable and detected on BLI. The basal rate of growth of these tumours was established for 1 week, followed daily intratumoural (i.t.) injections of DMSO, 10mM D1 or D2 dissolved in 100 ml of 5% dextrose for 5 weeks. Effects on tumor growth were serially followed by BLI (shown in e after 5 weeks of daily i.t. injections) and graphically represented as fold change±s.d. over bioluminescence measured at the start of treatment (f). (g) AR was immunoprecipitated from mouse tumors by incubating extracts with an AR antibody conjugated to rabbit IgG DynaBeads for 60 min at 4 _C. Immunocomplexes were resolved by SDS–polyacrylamide gel electrophoresis and blots hybridized for AR, PELP1 and actin. Input is shown in the lower panels. Data in a–d and f are representative of three independent experiments and is shown as mean±s.d., *Po0.05.

* We have obtained an IRB (attached) for human explant work on this project

* We have further optimized the utility of the human explant models in multiple publications, including

Ravindranathan et al, Nature Communications 2013
Centenera et al, Nature Rev Urol, 2013
Schiewer et al, Cancer Discovery, 2012
Centenera et al, Clin Cancer Res, 2012
Wang et al., PNAS, 2014

* We have evaluated the effect of the peptidomimetics in human explant models and have shown that the explants block the androgen receptor signaling in prostate cancer and block the AR-PELP1 interaction. We are continuing work with our new generation peptidomimetics to evaluate if this effect is more specific for prostate cancer cells.
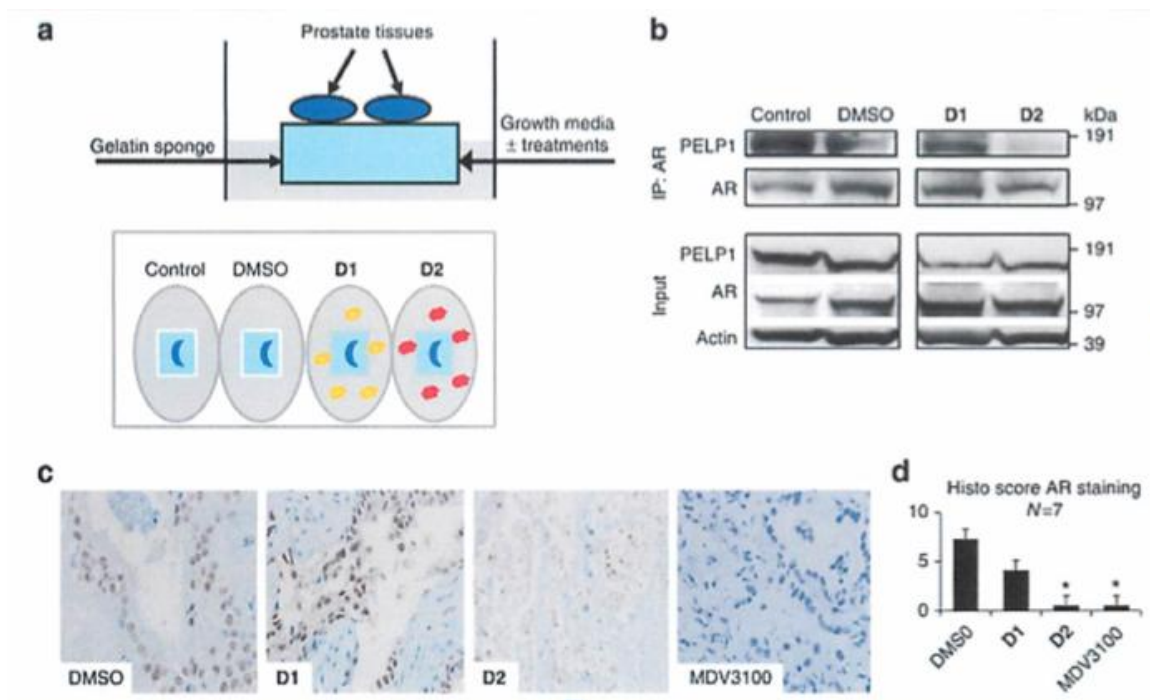
D2 inhibits AR–PELP1 interaction in prostate cancer cell explants. (a) Following radical prostatectomy, the extirpated prostate is bivalved and a core of tissue corresponding to the area of the tumour is removed by the pathologist. The tissue is then transferred to the laboratory and dissected into 1mm3 fragments. The fragments are then cultured on gelatin sponge submerged in media supplemented with 10% fetal calf serum. Following incubation with media for a defined time period (2 days), the explants are then processed for further evaluation. (b) Immunoprecipitation (IP) analyses of these prostate explants demonstrate the PPIs between AR and PELP1 in the presence of D1, DMSO but not D2 (100 nM). (c) Representative AR immunohistochemistry (IHC) staining in prostate cancer explants following incubation for 2 days in either complete media in the presence of 100nM DMSO, D1, D2 or 10 mM of MDV3100 reveals that D2 blocks nuclear AR expression. (d) Quantitation of AR immunostaining in prostate explants is shown for DMSO, D1, D2 or MDV3100 as a control (Po0.05). Data is shown as mean±s.d., n.7, *Po0.05.

With regard to the Statement of Work,
We had planned to

Specific Aim#1 To improve the design and synthesis of peptidomimetics for the LxxLL and WxxLF motif by using oligo-benzamide scaffolds that are highly specific for and can disrupt the AR-PELP-1 interaction, including

Development of LxxLL and WxxLF peptidomimetics by using a tris-benzamide scaffold
- Months 1-3 Designing and synthesizing trisbenzamide variants
- Months 3-12 Testing trisbenzamide variants variants *in vitro* and confirmation *in vivo* using co-immunoprecipitation experiments
- Months 13-18 Testing trisbenzamide variants on AR genomic signaling, proliferation
- Months 19-24 Evaluation of the data and publication of results

We believe that with the new synthetic platform, we are on schedule and are still working out the optimal reagents for activity. We have identified several tris-benzamides with increased activity and potency than our prior lead and are working to optimize this lead. We believe that our work to date will enable an even more robust analyses of trisbenzamides. We also are awaiting further studies to optimize the synthesis of lead peptidomimetics with potency <10nM. We believe that with more potent peptidomimetics, we will be able to validate assays in SA#2 and SA#3.

Specific Aim 2: To mechanistically characterize the ability of the peptidomimetics to modulate AR signaling in PCa cells, including the
Effect on genomic signaling and AR-modulated gene expression signatures

- Months 1-9 Testing peptidomimetics on LD and LI activity in Q PCR analyses
- Months 10-18 Microarray evaluation and analyses
- Months 19-24 Evaluation of the data and publication of results

Effect on nuclear translocation of AR
- Months 1-9 Optimization of nuclear translocation assays using confocal microscopy
- Months 10-14 Evaluation of effect of peptidomimetics on AR nuclear translocation
- Months 15-24 Biochemical validation of results from confocal experiments
- Months 25-27 Evaluation of the data and publication of results

We have developed a robust panel of genes for Q-PCR analyses but need to further validate peptidomimetics from Specific Aim#1 prior to validation by microarray and test effect on AR nuclear translocation. We are about two months behind on schedule on this aim, although we have optimized assays for validation.

Specific Aim 3: To study the effect of peptidomimetics on AR signaling in PCa cells in vivo, including the
Effect on CWR22v1 xenografts
- Months 7-12 Animal experiments with LD pathway
- Months 13-18 validation of LD pathway with biochemical studies
- Months 19-24 Animal experiments with LI pathway
- Months 25-33 validation of LI pathway with biochemical studies
- Months 33-36 Evaluation of the data and publication of results

Effect on human explants
- Months 1-32 Explant experiments
- Months 1-18 validation of LD pathway with biochemical studies
- Months 7-24 validation of LI pathway with biochemical studies
- Months 25-36 Evaluation of genetic signatures induced by LD and LI pathways
- Months 33-36 Evaluation of the data and publication of results

We have further validated the explants and have moved significantly beyond our initial plan on validation of the LD pathway with biochemical studies. We have published extensively on the explant model system and have developed significant expertise in this matter. We will start the animal experiments later this year to validate the effect on the LD and LI pathway.

Key Research Accomplishments

1. We have established a synthetic procedure that has dramatically enhanced our ability to generate a large number of peptidomimetics

2. We have designed, synthesized and tested 23 tris-benzamide analogues derived from the leading D2 compound.

3. We have generated tris-benzamide compounds with differential potency, selectivity and activity.

4. We have developed a robust panel of genes for AR signaling that is reflective of the clinical findings.

5. We have validated the efficacy of the peptidomimetics in animal models.

6. We have shown that these peptidomimetics are orally bioavailable with a half-life of 4 hours.

7. We have obtained an IRB (attached) for human explant work on this project

8. We have further optimized the utility of the human explant models in multiple publications, including Ravindranathan et al, Nature Communications 2013 Centenera et al, Nature Rev Urol, 2013 Schiewer et al, Cancer Discovery, 2012 Centenera et al, Clin Cancer Res, 2012

9. We have evaluated the effect of the peptidomimetics in human explant models and have validated this approach

10. We have published our lead paper on peptidomimetics, Ravindranathan et al, Nature Communications, 2013

Reportable Outcomes

1. We have presented this work at the Gordon conference, the Lorne cancer conference, the EMBO meeting on nuclear receptors and at the AUA SBUR meeting

2. We have published our lead paper on peptidomimetics, Ravindranathan et al, Nature Communications, 2013

3. Our patents on peptidomimetics were licensed by a pharmaceutical company to help further development for clinical trials

4. We have further optimized the utility of the human explant models in multiple publications, including Ravindranathan et al, Nature Communications 2013 Centenera et al, Nature Rev Urol, 2013 Schiewer et al, Cancer Discovery, 2012 Centenera et al, Clin Cancer Res, 2012

5. We applied for and received the first DOD transformative grant (PI: Plymate) which are partly based on further discovery and development for clinical trials of peptidomimetics targeting the aberrant androgen receptor specifically the androgen receptor splice variants.

Conclusions

In the first year of funding, we have made tremendous strides in further developing peptidomimetics targeting the androgen receptor. In order to develop a more efficient synthesis, we retooled our entire synthetic platform to develop a simpler process with higher yields of compounds. This enabled us to create 23 peptidomimetics that we have since characterized in detail. We have identified 4 compounds that work better than the parent compound D2 and are currently optimizing approaches to increase potency of these compounds.   We have published a landmark paper on the peptidomimetics and have several other manuscripts in preparation for submission. We have optimized our explant protocol for human tissue evaluation and believe that we are making significant progress towards rationally designing agents targeting the androgen-dependent and androgen-independent pathways in prostate cancer. We have received additional funding for our work and are confident that we will move the process forward for peptidomimetics.

References

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2. Ravindranathan P, Lee TK, Yang L, Centenera MM, Butler L, Tilley WD, Hsieh JT, Ahn JM, Raj GV. Peptidomimetic targeting of critical androgen receptor-coregulator interactions in prostate cancer. Nat Commun. 2013;4:1923

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5. Chung PH, Gayed BA, Thoreson GR, Raj GV. Emerging drugs for prostate cancer. Expert Opin Emerg Drugs. 2013 Dec;18(4):533-50.

Appendices

Publications with DOD funding:

We have several manuscripts submitted with the funding from this grant. Several will be published in 2014.

Presentations with DOD funding
Lorne Cancer Conference program 2014
Rational targeting of the Androgen receptor interactome in Prostate Cancer

Preethi Ravindranathan, Wayne Tilley, JungMo Ahn and Ganesh V. Raj
Author Affiliations: Department of Urology, UT Southwestern at Dallas, Department of Chemistry, UT Dallas, and University of Adelaide.

Background: The Androgen receptor (AR) is the central driver of prostate cancer and AR signaling is intact across all stages of disease. The interaction of AR with protein cofactors is critical for its signaling: targeted disruption of these interactions may enable shutdown of AR signaling.

Methods: Using known crystal structure, modeled structure and imputed structure based models, peptide agents were rationally designed to block the interface between AR and critical cofactors in its interactome and tested for physiologic activity using prostate cancer cell lines, xenografts and primary tumor explants.

Results: Knowledge of the protein cofactors, their interacting motifs and structure of the interface are needed for optimal targeting of protein-protein interactions. Using an iterative rational design approach, we have been able to successfully disrupt three classes of the AR interactome:
1. Interactions where the protein cofactor, the motifs and the structure of the interface is known, (targeting AR-PELP1 interface through a helical LxxLL motif)
2. Interactions where the protein cofactor is known but the motifs and the structure of the interface is not known, (targeting AR-FoxA1 interaction) and
3. Interactions where the motif is known, but neither the protein cofactor nor the structure of the interface are known (only known is a critical motif on AR).
The design of initial compounds targeting the interactions in Class 1 was based on crystal structures, while those for Class 2 and Class 3 were based on either predicted or imputed (motif in different context) structures. The interaction between AR and proteins in each of these classes is disrupted by a targeted agent as evidenced by co-immunoprecipitation of endogenous protein cofactors and AR. The functional utility of these agents blocking the AR interactome on AR driven gene expression and proliferation has been validated for agents in Class 1, but is being validated for agents in Classes 2 and 3. In each case, using significant structural modeling, active agents were synthesized with a minimal use of synthesis of analogues.

Conclusions: The rational targeting of the AR interactome is feasible and may be a useful complement to traditional screening campaigns. We have demonstrated the utility of this approach to blocking the interface in three distinct classes of protein-protein interactions. Further validation/optimization of these drugs is needed prior to their clinical implementation.

References: Ravindranathan P, Lee TK, Yang L, Centenera MM, Butler L, Tilley WD, Hsieh JT, Ahn JM, Raj GV. Peptidomimetic targeting of critical androgen receptor-coregulator interactions in prostate cancer. Nat Commun. 2013;4:1923.

Talks

EMBO conference: Nuclear receptors and physiology 2013: Targeting the Androgen receptor in prostate cancer.

Gordon conference on Nuclear receptors, 2013

AUA annual meeting 2013: Targeting the ligand-dependent androgen receptor in prostate cancer